

1 **DEVICE FOR TRANSDERMAL ELECTROTRANSPORT**
2 **DELIVERY OF FENTANYL AND SUFENTANIL**

3
4 **TECHNICAL FIELD**
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6 The invention relates generally to improved electrotransport drug
7 delivery. Specifically, the invention relates to a device, composition and
8 method for improved electrotransport delivery of analgesic drugs, particularly
9 fentanyl and analogs of fentanyl. A composition is provided in the form of a
10 hydrogel formulation for use in an electrotransport device.

11
12 **BACKGROUND ART**
13

14 The transdermal delivery of drugs, by diffusion through the epidermis,
15 offers improvements over more traditional delivery methods, such as
16 subcutaneous injections and oral delivery. Transdermal drug delivery avoids
17 the hepatic first pass effect encountered with oral drug delivery. Transdermal
18 drug delivery also eliminates patient discomfort associated with subcutaneous
19 injections. In addition, transdermal delivery can provide more uniform
20 concentrations of drug in the bloodstream of the patient over time due to the
21 extended controlled delivery profiles of certain types of transdermal delivery
22 devices. The term "transdermal" delivery, broadly encompasses the delivery
23 of an agent through a body surface, such as the skin, mucosa, or nails of
24 an animal.

25 The skin functions as the primary barrier to the transdermal penetration
26 of materials into the body and represents the body's major resistance to the
27 transdermal delivery of therapeutic agents such as drugs. To date, efforts
28 have been focused on reducing the physical resistance or enhancing the
29 permeability of the skin for the delivery of drugs by passive diffusion.

1 Various methods for increasing the rate of transdermal drug flux have been
2 attempted, most notably using chemical flux enhancers.

3 Other approaches to increase the rates of transdermal drug delivery
4 include use of alternative energy sources such as electrical energy and
5 ultrasonic energy. Electrically assisted transdermal delivery is also referred to
6 as electrotransport. The term "electrotransport" as used herein refers
7 generally to the delivery of an agent (e.g., a drug) through a membrane,
8 such as skin, mucous membrane, or nails. The delivery is induced or aided
9 by application of an electrical potential. For example, a beneficial therapeutic
10 agent may be introduced into the systemic circulation of a human body by
11 electrotransport delivery through the skin. A widely used electrotransport
12 process, electromigration (also called iontophoresis), involves the electrically
13 induced transport of charged ions. Another type of electrotransport,
14 electroosmosis, involves the flow of a liquid, which liquid contains the agent to
15 be delivered, under the influence of an electric field. Still another type of
16 electrotransport process, electroporation, involves the formation of transiently-
17 existing pores in a biological membrane by the application of an electric field.
18 An agent can be delivered through the pores either passively (i.e., without
19 electrical assistance) or actively (i.e., under the influence of an electric
20 potential). However, in any given electrotransport process, more than one of
21 these processes, including at least some "passive" diffusion, may be
22 occurring simultaneously to a certain extent. Accordingly, the term
23 "electrotransport", as used herein, should be given its broadest possible
24 interpretation so that it includes the electrically induced or enhanced transport
25 of at least one agent, which may be charged, uncharged, or a mixture thereof,
26 whatever the specific mechanism or mechanisms by which the agent actually
27 is transported.

1 Electrotransport devices use at least two electrodes that are in
2 electrical contact with some portion of the skin, nails, mucous membrane,
3 or other surface of the body. One electrode, commonly called the "donor"
4 electrode, is the electrode from which the agent is delivered into the body.
5 The other electrode, typically termed the "counter" electrode, serves to close
6 the electrical circuit through the body. For example, if the agent to be
7 delivered is positively charged, i.e., a cation, then the anode is the donor
8 electrode, while the cathode is the counter electrode which serves to
9 complete the circuit. Alternatively, if an agent is negatively charged,
10 i.e., an anion, the cathode is the donor electrode and the anode is the
11 counter electrode. Additionally, both the anode and cathode may be
12 considered donor electrodes if both anionic and cationic agent ions,
13 or if uncharged dissolved agents, are to be delivered.

14 Furthermore, electrotransport delivery systems generally require at
15 least one reservoir or source of the agent to be delivered to the body.
16 Examples of such donor reservoirs include a pouch or cavity, a porous
17 sponge or pad, and a hydrophilic polymer or a gel matrix. Such donor
18 reservoirs are electrically connected to, and positioned between, the anode or
19 cathode and the body surface, to provide a fixed or renewable source of one
20 or more agents or drugs. Electrotransport devices also have an electrical
21 power source such as one or more batteries. Typically at any one time,
22 one pole of the power source is electrically connected to the donor electrode,
23 while the opposite pole is electrically connected to the counter electrode.
24 Since it has been shown that the rate of electrotransport drug delivery is
25 approximately proportional to the electric current applied by the device,
26 many electrotransport devices typically have an electrical controller that
27 controls the voltage and/or current applied through the electrodes, thereby
28 regulating the rate of drug delivery. These control circuits use a variety of
29 electrical components to control the amplitude, polarity, timing, waveform

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1 shape, etc. of the electric current and/or voltage supplied by the power
2 source. See, for example, McNichols et al., U.S. Patent 5,047,007.

3 To date, commercial transdermal electrotransport drug delivery devices
4 (e.g., the Phoresor, sold by Iomed, Inc. of Salt Lake City, UT; the Dupel
5 Iontophoresis System sold by Empi, Inc. of St. Paul, MN; the Webster Sweat
6 Inducer, model 3600, sold by Wescor, Inc. of Logan, UT) have generally
7 utilized a desk-top electrical power supply unit and a pair of skin contacting
8 electrodes. The donor electrode contains a drug solution while the counter
9 electrode contains a solution of a biocompatible electrolyte salt. The power
10 supply unit has electrical controls for adjusting the amount of electrical current
11 applied through the electrodes. The "satellite" electrodes are connected to
12 the electrical power supply unit by long (e.g., 1-2 meters) electrically
13 conductive wires or cables. The wire connections are subject to
14 disconnection and limit the patient's movement and mobility. Wires between
15 electrodes and controls may also be annoying or uncomfortable to the patient.
16 Other examples of desk-top electrical power supply units which use "satellite"
17 electrode assemblies are disclosed in Jacobsen et al., U.S. Patent 4,141,359
18 (see Figures 3 and 4); LaPrade, U.S. Patent 5,006,108 (see Figure 9); and
19 Maurer et al., U.S. Patent 5,254,081.

20 More recently, small self-contained electrotransport delivery devices
21 have been proposed to be worn on the skin, sometimes unobtrusively
22 under clothing, for extended periods of time. Such small self-contained
23 electrotransport delivery devices are disclosed for example in
24 Tapper, U.S. Patent 5,224,927; Sibalis, et al., U.S. Patent 5,224,928;
25 and Haynes et al., U.S. Patent 5,246,418.

26 There have recently been suggestions to utilize electrotransport
27 devices having a reusable controller which is adapted for use with multiple
28 drug-containing units. The drug-containing units are simply disconnected
29 from the controller when the drug becomes depleted and a fresh drug-
30 containing unit is thereafter connected to the controller. In this way,

1 the relatively more expensive hardware components of the device
2 (e.g., batteries, LED's, circuit hardware, etc.) can be contained within the
3 reusable controller, and the relatively less expensive donor reservoir and
4 counter reservoir matrices can be contained in the single use/disposable
5 drug-containing unit, thereby bringing down the overall cost of
6 electrotransport drug delivery. Examples of electrotransport devices
7 comprised of a reusable controller, removably connected to a drug-containing
8 unit are disclosed in Sage, Jr. et al., U.S. Patent 5,320,597; Sibalis,
9 U.S. Patent 5,358,483; Sibalis et al., U.S. Patent 5,135,479 (Fig. 12);
10 and Devane et al., UK Patent Application 2 239 803.

11 In further development of electrotransport devices, hydrogels have
12 become particularly favored for use as the drug and electrolyte reservoir
13 matrices, in part, due to the fact that water is the preferred liquid solvent for
14 use in electrotransport drug delivery due to its excellent biocompatibility
15 compared with other liquid solvents such as alcohols and glycols.

16 Hydrogels have a high equilibrium water content and can quickly absorb
17 water. In addition, hydrogels tend to have good biocompatibility with the skin
18 and with mucosal membranes.

19 Of particular interest in transdermal delivery is the delivery of analgesic
20 drugs for the management of moderate to severe pain. Control of the rate
21 and duration of drug delivery is particularly important for transdermal delivery
22 of analgesic drugs to avoid the potential risk of overdose and the discomfort
23 of an insufficient dosage.

24 One class of analgesics that has found application in a transdermal
25 delivery route is the synthetic opiates, a group of 4-aniline piperidines.
26 The synthetic opiates, e.g., fentanyl and certain of its derivatives such as
27 sufentanil, are particularly well-suited for transdermal administration.
28 These synthetic opiates are characterized by their rapid onset of analgesia,
29 high potency, and short duration of action. They are estimated to be 80 and

1 800 times, respectively, more potent than morphine. These drugs are weak
2 bases, i.e., amines, whose major fraction is cationic in acidic media.

3 In an *in vivo* study to determine plasma concentration, Thysman and
4 Preat (*Anesth. Analg.* 77 (1993) pp. 61-66) compared simple diffusion of
5 fentanyl and sufentanil to electrotransport delivery in citrate buffer at pH 5.
6 Simple diffusion did not produce any detectable plasma concentration.
7 The plasma levels attainable depended on the maximum flux of the drug that
8 can cross the skin and the drug's pharmacokinetic properties, such as
9 clearance and volume of distribution. Electrotransport delivery was reported
10 to have significantly reduced lag time (i.e., time required to achieve peak
11 plasma levels) as compared to passive transdermal patches
12 (1.5 h versus 14 h). The researchers' conclusions were that electrotransport
13 of these analgesic drugs can provide more rapid control of pain than classical
14 patches, and a pulsed release of drug (by controlling electrical current)
15 was comparable to the constant delivery of classical patches. See, also,
16 e.g., Thysman et al. *Int. J. Pharma.*, 101 (1994) pp. 105-113; V. Préat et al.
17 *Int. J. Pharma.*, 96 (1993) pp. 189-196 (sufentanil); Gourlav et al. *Pain*,
18 37 (1989) pp. 193-202 (fentanyl); Sebel et al. *Eur. J. Clin. Pharmacol.* 32
19 (1987) pp. 529-531 (fentanyl and sufentanil). Passive, i.e., by diffusion, and
20 electrically-assisted transdermal delivery of narcotic analgesic drugs, such as
21 fentanyl, to induce analgesia, have also both been described in the patent
22 literature. See, for example, Gale et al., U.S. Patent 4,588,580, and
23 Theeuwes et al., U.S. Patent 5,232,438.

24 In the last several years, management of post-operative pain has
25 looked to delivery systems other than electrotransport delivery. Particular
26 attention has been given to devices and systems which permit, within
27 predetermined limits, the patient to control the amount of analgesic the patient
28 receives. The experience with these types of devices has generally been that
29 patient control of the administration of analgesic has resulted in the
30 administration of less analgesic to the patient than would have been

1 administered were the dosage prescribed by a physician. Self-administered
2 or patient controlled self-administration has become known (and will be
3 referred to herein) as patient-controlled analgesia (PCA).

4 Known PCA devices are typically electromechanical pumps which
5 require large capacity electrical power sources, e.g., alternating current or
6 multiple large capacity battery packs which are bulky. Due to their bulk
7 and complexity, commercially available PCA devices generally require
8 the patient to be confined to a bed, or some other essentially fixed location.

9 Known PCA devices deliver drug to the patient by means of an intravenous
10 line or a catheter which must be inserted into the intended vein, artery or
11 other organ by a qualified medical technician. This technique requires
12 that the skin barrier be breached in order to administer the analgesic.

13 (See, Zdeb U.S. Patent 5,232,448). Thus, as practiced using commercially
14 available PCA devices, PCA requires the presence of highly skilled medical
15 technicians to initiate and supervise the operation of the PCA device along
16 with its attendant risk of infection. Further, commercially available PCA
17 devices themselves are somewhat painful to use by virtue of their
18 percutaneous (i.e., intravenous or subcutaneous) access.

19 The art has produced little in the way of transdermal electrotransport
20 devices that can compete with the conventional PCAs in terms of the amount
21 of drug delivered to achieve adequate analgesia and in a patient controlled
22 manner. Further, little progress has been made to provide a hydrogel
23 formulation for analgesic electrotransport, particularly fentanyl transdermal
24 electrotransport delivery, that has long term stability and has performance
25 characteristics comparable to the patient controlled electromechanical pumps
26 for, e.g., intravenous delivery of analgesic. There is need to provide an
27 analgesic formulation in a suitable device to take advantage of the
28 convenience of electrotransport delivery in a small, self-contained,
29 patient-controlled device.

1 DESCRIPTION OF THE INVENTION

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3 The present invention provides a device for improved transdermal
4 electrotransport delivery of fentanyl and analogs of fentanyl, particularly
5 sufentanil. As such, the device of the present invention provides a greater
6 degree of efficiency in electrotransport delivery of analgesic fentanyl or
7 sufentanil, concomitantly providing a greater measure of patient safety and
8 comfort in pain management. The foregoing, and other advantages of the
9 present invention, are provided by a device for delivering fentanyl or
10 sufentanil through a body surface (e.g., intact skin) by electrotransport,
11 the device having a anodic donor reservoir containing an at least partially
12 aqueous solution of a fentanyl/sufentanil salt.

13 The present invention concerns a device for administering fentanyl or
14 sufentanil by transdermal electrotransport in order to treat moderate-to-severe
15 pain associated with major surgical procedures. A transdermal
16 electrotransport dose of about 20 μ g to about 60 μ g of fentanyl, delivered
17 over a delivery interval of up to about 20 minutes, is therapeutically effective
18 in treating moderate-to-severe post-operative pain in human patients having
19 body weights above about 35 kg. Preferably, the amount of fentanyl
20 delivered is about 35 μ g to about 45 μ g over a delivery interval of about
21 5 to 15 minutes, and most preferably the amount of fentanyl delivered is
22 about 40 μ g over a delivery interval of about 10 minutes. Since fentanyl
23 has a relatively short distribution half life once delivered into a human body
24 (i.e., about 3 hours), the device for inducing analgesia preferably includes
25 means for maintaining the analgesia so induced. Thus the device for
26 transdermally delivering fentanyl by electrotransport preferably includes
27 means for delivering at least 1 additional, more preferably about 10 to 100
28 additional, and most preferably about 20 to 80 additional, like dose(s) of
29 fentanyl over subsequent like delivery interval(s) over a 24 hour period. The
30 ability to deliver multiple identical doses from a transdermal electrotransport

1 fentanyl delivery device also provides the capability of pain management to a
2 wider patient population, in which different patients require different amounts
3 of fentanyl to control their pain. By providing the capability of administering
4 multiple small transdermal electrotransport fentanyl doses, the patients can
5 titrate themselves to administer only that amount of fentanyl which is needed
6 to control their pain, and no more.

7 Other advantages and a fuller appreciation of specific adaptations,
8 compositional variations, and physical attributes of the present invention can
9 be learned from an examination of the following drawings, detailed
10 description, examples, and appended claims.

11

12 BRIEF DESCRIPTION OF THE DRAWINGS

13

14 The present invention is hereinafter described in conjunction with the
15 appended drawings, in which:

16 Figure 1 is a perspective exploded view of an electrotransport drug
17 delivery device in accordance with the present invention;

18 Figure 2 is a graph illustrating quality of analgesia in patients
19 administered with transdermal electrotransport fentanyl as a function of time;
20 and

21 Figure 3 is a graph illustrating pain intensity experienced by patients
22 administered transdermal electrotransport fentanyl as a function of time.

23

24 MODES FOR CARRYING OUT THE INVENTION

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26 The present invention provides a fentanyl or sufentanil salt
27 electrotransport delivery device, and a method of using same, to achieve a
28 systemic analgesic effect which is comparable to the effect achieved in known
29 IV accessed patient controlled analgesic pumps. The present invention
30 provides an electrotransport delivery device for delivering fentanyl or

1 sufentanil through a body surface, e.g., skin, to achieve the analgesic effect.
2 The fentanyl or sufentanil salt is provided in a donor reservoir of an
3 electrotransport delivery device, preferably as an aqueous salt solution.

4 The dose of fentanyl delivered by transdermal electrotransport is about
5 20 µg to about 60 µg over a delivery time of up to about 20 minutes in human
6 patients having body weights of 35 kg or greater. Preferred is a dosage of
7 about 35 µg to about 45 µg, and most preferred is a dosage of about 40 µg
8 for the delivery period. The device of the invention further preferably includes
9 means for delivering about 10 to 100, and more preferably about 20 to 80
10 additional like doses over a period of 24 hours in order to achieve and
11 maintain the analgesic effect.

12 The dose of sufentanil delivered by transdermal electrotransport is
13 about 2.3 µg to about 7.0 µg over a delivery time of up to about 20 minutes in
14 human patients having a body weights of 35 kg or greater. Preferred is a
15 dosage of about 4 µg to about 5.5 µg, and most preferred is a dosage of
16 about 4.7 µg for the delivery period. The device of the invention further
17 preferably includes means for delivering about 10 to 100, and more
18 preferably about 20 to 80 additional like doses over a period of 24 hours in
19 order to achieve and maintain the analgesic effect.

20 The fentanyl/sufentanil salt-containing anodic reservoir formulation for
21 transdermally delivering the above mentioned doses of fentanyl/sufentanil by
22 electrotransport is preferably comprised of an aqueous solution of a water
23 soluble fentanyl/sufentanil salt such as HCl or citrate salts. Most preferably,
24 the aqueous solution is contained within a hydrophilic polymer matrix such as
25 a hydrogel matrix. The fentanyl/sufentanil salt is present in an amount
26 sufficient to deliver the above mentioned doses transdermally by
27 electrotransport over a delivery period of up to about 20 minutes, to achieve a
28 systemic analgesic effect. The fentanyl/sufentanil salt typically comprises
29 about 1 to 10 wt% of the donor reservoir formulation (including the weight of
30 the polymeric matrix) on a fully hydrated basis, and more preferably about

1 1 to 5 wt% of the donor reservoir formulation on a fully hydrated basis.
2 Although not critical to this aspect of the present invention, the applied
3 electrotransport current density is typically in the range of about
4 50 to 150 μ A/cm² and the applied electrotransport current is typically
5 in the range of about 150 to 240 μ A.

The anodic fentanyl/sufentanil salt-containing hydrogel can suitably be made of a any number of materials but preferably is comprised of a hydrophilic polymeric material, preferably one that is polar in nature so as to enhance the drug stability. Suitable polar polymers for the hydrogel matrix comprise a variety of synthetic and naturally occurring polymeric materials. A preferred hydrogel formulation contains a suitable hydrophilic polymer, a buffer, a humectant, a thickener, water and a water soluble fentanyl or sufentanil salt (e.g., HCl salt). A preferred hydrophilic polymer matrix is polyvinyl alcohol such as a washed and fully hydrolyzed polyvinyl alcohol (PVOH), e.g., Mowiol 66-100 commercially available from Hoechst Aktiengesellschaft. A suitable buffer is an ion exchange resin which is a copolymer of methacrylic acid and divinylbenzene in both an acid and salt form. One example of such a buffer is a mixture of Polacrilin (the copolymer of methacrylic acid and divinyl benzene available from Rohm & Haas, Philadelphia, PA) and the potassium salt thereof. A mixture of the acid and potassium salt forms of Polacrilin functions as a polymeric buffer to adjust the pH of the hydrogel to about pH 6. Use of a humectant in the hydrogel formulation is beneficial to inhibit the loss of moisture from the hydrogel. An example of a suitable humectant is guar gum. Thickeners are also beneficial in a hydrogel formulation. For example, a polyvinyl alcohol thickener such as hydroxypropyl methylcellulose (e.g., Methocel K100MP available from Dow Chemical, Midland, MI) aids in modifying the rheology of a hot polymer solution as it is dispensed into a mold or cavity.

1 The hydroxypropyl methylcellulose increases in viscosity on cooling and
2 significantly reduces the propensity of a cooled polymer solution to overfill
3 the mold or cavity.

4 In one preferred embodiment, the anodic fentanyl/sufentanil salt-
5 containing hydrogel formulation comprises about 10 to 15 wt% polyvinyl
6 alcohol, 0.1 to 0.4 wt% resin buffer, and about 1 to 2 wt% fentanyl or
7 sufentanil salt, preferably the hydrochloride salt. The remainder is water and
8 ingredients such as humectants, thickeners, etc. The polyvinyl alcohol
9 (PVOH)-based hydrogel formulation is prepared by mixing all materials,
10 including the fentanyl or sufentanil salt, in a single vessel at elevated
11 temperatures of about 90 °C to 95 °C for at least about 0.5 hr. The hot mix
12 is then poured into foam molds and stored at freezing temperature of
13 about -35 °C overnight to cross-link the PVOH. Upon warming to ambient
14 temperature, a tough elastomeric gel is obtained suitable for fentanyl
15 electrotransport.

16 The hydrogel formulations are used in an electrotransport device such
17 as described hereinafter. A suitable electrotransport device includes an
18 anodic donor electrode, preferably comprised of silver, and a cathodic counter
19 electrode, preferably comprised of silver chloride. The donor electrode is in
20 electrical contact with the donor reservoir containing the aqueous solution of a
21 fentanyl/sufentanil salt. As described above, the donor reservoir is preferably
22 a hydrogel formulation. The counter reservoir also preferably comprises a
23 hydrogel formulation containing a (e.g., aqueous) solution of a biocompatible
24 electrolyte, such as citrate buffered saline. The anodic and cathodic hydrogel
25 reservoirs preferably each have a skin contact area of about 1 to 5 cm² and
26 more preferably about 2 to 3 cm². The anodic and cathodic hydrogel
27 reservoirs preferably have a thickness of about 0.05 to 0.25 cm, and
28 more preferably about 0.15 cm. The applied electrotransport current is

1 about 150 μ A to about 240 μ A, depending on the analgesic effect desired.

2 Most preferably, the applied electrotransport current is substantially
3 constant DC current during the dosing interval.

4 Reference is now made to FIG. 1 which depicts an exemplary
5 electrotransport device which can be used in accordance with the present
6 invention. FIG. 1 shows a perspective exploded view of an electrotransport
7 device 10 having an activation switch in the form of a push button switch 12
8 and a display in the form of a light emitting diode (LED) 14. Device 10
9 comprises an upper housing 16, a circuit board assembly 18, a lower housing
10 20, anode electrode 22, cathode electrode 24, anode reservoir 26, cathode
11 reservoir 28 and skin-compatible adhesive 30. Upper housing 16 has lateral
12 wings 15 which assist in holding device 10 on a patient's skin. Upper housing
13 16 is preferably composed of an injection moldable elastomer (e.g., ethylene
14 vinyl acetate). Printed circuit board assembly 18 comprises an integrated
15 circuit 19 coupled to discrete electrical components 40 and battery 32.
16 Circuit board assembly 18 is attached to housing 16 by posts (not shown in
17 FIG. 1) passing through openings 13a and 13b, the ends of the posts being
18 heated/melted in order to heat stake the circuit board assembly 18 to the
19 housing 16. Lower housing 20 is attached to the upper housing 16 by means
20 of adhesive 30, the upper surface 34 of adhesive 30 being adhered to both
21 lower housing 20 and upper housing 16 including the bottom surfaces of
22 wings 15.

23 Shown (partially) on the underside of circuit board assembly 18 is
24 a battery 32, which is preferably a button cell battery and most preferably
25 a lithium cell. Other types of batteries may also be employed to power
26 device 10.

1 The circuit outputs (not shown in FIG. 1) of the circuit board
2 assembly 18 make electrical contact with the electrodes 24 and 22
3 through openings 23,23' in the depressions 25,25' formed in lower
4 housing, by means of electrically conductive adhesive strips 42,42'.
5 Electrodes 22 and 24, in turn, are in direct mechanical and electrical
6 contact with the top sides 44',44 of reservoirs 26 and 28. The bottom sides
7 46',46 of reservoirs 26,28 contact the patient's skin through the openings
8 29',29 in adhesive 30. Upon depression of push button switch 12, the
9 electronic circuitry on circuit board assembly 18 delivers a predetermined
10 DC current to the electrodes/reservoirs 22,26 and 24,28 for a delivery interval
11 of predetermined length, e.g., about 10 minutes. Preferably, the device
12 transmits to the user a visual and/or audible confirmation of the onset of the
13 drug delivery, or bolus, interval by means of LED 14 becoming lit and/or an
14 audible sound signal from, e.g., a "beeper". Analgesic drug, e.g. fentanyl, is
15 then delivered through the patient's skin, e.g., on the arm, for the
16 predetermined (e.g., 10 minute) delivery interval. In practice, a user receives
17 feedback as to the onset of the drug delivery interval by visual (LED 14
18 becomes lit) and/or audible signals (a beep from the "beeper").

19 Anodic electrode 22 is preferably comprised of silver and cathodic
20 electrode 24 is preferably comprised of silver chloride. Both reservoirs
21 26 and 28 are preferably comprised of polymer hydrogel materials as
22 described herein. Electrodes 22, 24 and reservoirs 26, 28 are retained by
23 lower housing 20. For fentanyl and sufentanil salts, the anodic reservoir 26 is
24 the "donor" reservoir which contains the drug and the cathodic reservoir 28
25 contains a biocompatible electrolyte.

26 The push button switch 12, the electronic circuitry on circuit board
27 assembly 18 and the battery 32 are adhesively "sealed" between upper
28 housing 16 and lower housing 20. Upper housing 16 is preferably composed
29 of rubber or other elastomeric material. Lower housing 20 is preferably
30 composed of a plastic or elastomeric sheet material (e.g., polyethylene) which

1 can be easily molded to form depressions 25,25' and cut to form openings
2 23,23'. The assembled device 10 is preferably water resistant (i.e., splash
3 proof) and is most preferably waterproof. The system has a low profile that
4 easily conforms to the body thereby allowing freedom of movement at, and
5 around, the wearing site. The anode/drug reservoir 26 and the cathode/salt
6 reservoir 28 are located on the skin-contacting side of device 10 and are
7 sufficiently separated to prevent accidental electrical shorting during normal
8 handling and use.

9 The device 10 adheres to the patient's body surface (e.g., skin)
10 by means of a peripheral adhesive 30 which has upper side 34 and body-
11 contacting side 36. The adhesive side 36 has adhesive properties which
12 assures that the device 10 remains in place on the body during normal user
13 activity, and yet permits reasonable removal after the predetermined
14 (e.g., 24-hour) wear period. Upper adhesive side 34 adheres to lower
15 housing 20 and retains the electrodes and drug reservoirs within housing
16 depressions 25,25' as well as retains lower housing 20 attached to upper
17 housing 16.

18 The push button switch 12 is located on the top side of device 10 and
19 is easily actuated through clothing. A double press of the push button switch
20 12 within a short period of time, e.g., three seconds, is preferably used to
21 activate the device 10 for delivery of drug, thereby minimizing the likelihood of
22 inadvertent actuation of the device 10.

23 Upon switch activation an audible alarm signals the start of drug
24 delivery, at which time the circuit supplies a predetermined level of
25 DC current to the electrodes/reservoirs for a predetermined (e.g., 10 minute)
26 delivery interval. The LED 14 remains "on" throughout the delivery interval
27 indicating that the device 10 is in an active drug delivery mode. The battery
28 preferably has sufficient capacity to continuously power the device 10 at the
29 predetermined level of DC current for the entire (e.g., 24 hour) wearing
30 period.

1 Preferably, the concentration of fentanyl or sufentanil in solution in the
2 donor-reservoir is maintained at or above the level at which the transdermal
3 electrotransport fentanyl/sufentanil flux is independent of drug concentration
4 in the donor reservoir during the electrotransport drug delivery period.
5 Transdermal electrotransport fentanyl flux begins to become dependent upon
6 the concentration of the fentanyl salt in aqueous solution as the fentanyl salt
7 concentration falls below about 11 to 16 mM. The 11 to 16 mM concentration
8 is calculated based only on the volume of liquid solvent used in the donor
9 reservoir, not on the total volume of the reservoir. In other words,
10 the 11 to 16 mM concentration does not include the volume of the
11 reservoir which is represented by the reservoir matrix (e.g., hydrogel
12 or other matrix) material. Furthermore, the 11 to 16 mM concentration is
13 based upon the number of moles of fentanyl salt, not the equivalent number
14 of moles of fentanyl free base, which is contained in the donor reservoir
15 solution. For fentanyl HCl, the 11 to 16 mM concentration is equivalent to
16 about 4 to 6 mg/mL. Other fentanyl salts (e.g., fentanyl citrate) will have
17 slightly differing weight based concentration ranges based on the difference in
18 the molecular weight of the counter ion of the particular fentanyl salt in
19 question. As the fentanyl salt concentration falls to about 11 to 16 mM, the
20 fentanyl transdermal electrotransport flux begins to significantly decline, even
21 if the applied electrotransport current remains constant. Thus, to ensure a
22 predictable fentanyl flux with a particular level of applied electrotransport
23 current, the fentanyl salt concentration in the solution contained in the donor
24 reservoir is preferably maintained above about 11 mM, and more preferably
25 above about 16 mM. In addition to fentanyl, water soluble salts of sufentanil
26 also have minimum aqueous solution concentrations below which the
27 transdermal electrotransport flux becomes dependent on concentration of the
28 sufentanil salt in solution. The minimum concentration for sufentanil is about
29 1.7 mM, which for sufentanil citrate is equivalent to about 1 mg/mL.

1 Since fentanyl and sufentanil are both bases, the salts of fentanyl
2 and sufentanil are typically acid addition salts, e.g., citrate salts, hydrochloride
3 salts, etc. The acid addition salts of fentanyl typically have water solubilities
4 of about 25 to 30 mg/mL. The acid addition salts of sufentanil typically
5 have water solubilities of about 45 to 50 mg/mL. When these salts are
6 placed in solution (e.g., aqueous solution), the salts dissolve and form
7 protonated fentanyl or sufentanil cations and counter (e.g., citrate or chloride)
8 anions. As such, the fentanyl/sufentanil cations are delivered from the
9 anodic electrode of an electrotransport delivery device. Silver anodic
10 electrodes have been proposed for transdermal electrotransport delivery
11 as a way to maintain pH stability in the anodic reservoir. See for
12 example, Untereker et al U.S. Patent 5,135,477 and Petelenz et al
13 U.S. Patent 4,752,285. These patents also recognize one of the
14 shortcomings of using a silver anodic electrode in an electrotransport
15 delivery device, namely that the application of current through the silver
16 anode causes the silver to become oxidized ($\text{Ag} \rightarrow \text{Ag}^+ + \text{e}^-$) thereby forming
17 silver cations which compete with the cationic drug for delivery into the skin
18 by electrotransport. Silver ion migration into the skin results in a transient
19 epidermal discoloration (TED) of the skin. In accordance with the teachings in
20 these patents, the cationic fentanyl and sufentanil are preferably formulated
21 as a halide salt (e.g., hydrochloride salt) so that any electrochemically-
22 generated silver ions will react with the drug counter ions (i.e., halide ions)
23 to form a substantially insoluble silver halide ($\text{Ag}^+ + \text{X}^- \rightarrow \text{AgX}$). In addition to
24 these patents, Phipps et al, WO 95/27530 teaches the use of supplementary
25 chloride ion sources in the form of high molecular weight chloride resins in the
26 donor reservoir of a transdermal electrotransport delivery device. These
27 resins are highly effective at providing sufficient chloride for preventing silver
28 ion migration, and the attendant skin discoloration when delivering fentanyl or
29 sufentanil transdermally by electrotransport using a silver anodic electrode.

The present invention is further explained by the following examples which are illustrative of, but do not limit the scope of, the present invention.

EXAMPLE 1

The following studies were conducted to determine the transdermal electrotransport dosing level required to achieve an acceptable level of analgesia in human patients suffering from moderate to severe post-operative pain. The study was conducted in 132 post-operative male and female patients who were expected to have moderate to severe pain after surgery, including orthopedic (shoulder, knee, long bone) and abdominal (urological, gynecological) surgeries. The patients wore one of two different electrotransport fentanyl HCl delivery devices on the upper arm for 24 hours following surgery. Both devices applied electrotransport current for a delivery interval of 10 minutes upon activating a push button switch on the device. The first device, worn by 79 of the 132 patients, applied an electrotransport current of 150 µA which delivered an average fentanyl dose of 25 µg over the 10 minute delivery interval. The second device, worn by 53 of the 132 patients, applied an electrotransport current of 240 µA which delivered an average fentanyl dose of 40 µg over the 10 minute delivery interval.

In both devices, the patients could self-administer up to 6 doses every hour. Patients using the first (i.e., 25 µg dose) device could apply a maximum of 144 doses. Patients using the second (i.e., 40 µg dose) device were allowed to apply up to a maximum number of 80 doses.

Both devices were two-part systems which included a reusable electronic controller and a single use/disposable drug-containing unit. Each drug unit contained an anodic fentanyl HCl-containing donor gel and a cathodic saline-containing counter gel. All gels had a skin contact area of 2 cm² and a thickness of 0.16 cm. The approximate weight of the donor gels was 350 mg. The anodic donor gels in the 25 µg dose and 40 µg dose

1 systems were the same size and composition, only the applied
2 electrotransport current level was different. The cathodic counter electrode
3 assemblies each had a PVOH based gel which contained citrate buffered
4 saline. A silver chloride cathodic electrode was laminated to one surface of
5 the counter gel. The 25 µg and 40 µg dose anodic gels had the following
6 composition:

7

8	<u>Material</u>	(wt%)
9	Water	73.2
10	PVOH	10.0
11	Fentanyl HCl	1.4
12	Polacrilin	0.3
13	Polacrilin potassium	0.1
14	Glycerin	5.0
15	Cholestyramine resin	10.0

16

17 All patients were initially titrated to an acceptable level of analgesia
18 with intravenous (IV) fentanyl in the recovery room immediately following
19 surgery. Within 3 hours after surgery when the patients had met the usual
20 institutional standards for discharge from the recovery room and were able to
21 operate their worn electrotransport delivery device, the patients were moved
22 to a ward where they could self administer fentanyl by transdermal
23 electrotransport for the management of their pain. In the event the
24 electrotransport fentanyl delivery regimen was insufficient to control pain,
25 the patients were retitrated with supplemental fentanyl through
26 IV administration to achieve adequate analgesia.

27 In the 25 µg dose group, 38 of 79 patients (i.e., 48%) required no
28 supplemental IV fentanyl after leaving the recovery room. In the 40 µg dose
29 group, 47 of 53 patients (i.e., 89%) required no supplemental IV fentanyl after
30 leaving the recovery room. Based on these percentages, it was determined

1 that the 25 µg dose regimen was sufficient to treat the pain associated with
2 these types of surgical procedures in about one-half of the patients; and the
3 40 µg dose regimen was sufficient to treat the pain associated with these
4 types of surgical procedures in about 90% of the patients tested. Because
5 the 25 µg dose regimen was analgesically effective for about half the patients,
6 lower dosing regimens of about 20 to 30 µg and preferably about 20 to 25 µg
7 of fentanyl over these same dosing intervals (i.e., up to 20 minutes) are also
8 effective, and less susceptible to unintentional over-dosing, in treating less
9 severe acute pain such as that experienced with hernia repair, kidney stones,
10 arthritis pain, laparoscopic procedures, and other conditions involving less
11 severe pain than that associated with major surgeries. The corresponding
12 lower dosing regimens for sufentanil are about 2.3 µg to about 3.5 µg, and
13 preferably about 2.3 µg to about 2.9 µg, delivered over these same dosing
14 intervals (i.e., up to 20 minutes).

15 Pain intensity was assessed at baseline immediately before activation
16 of the first on-demand dose and again at times 0.5, 1, 2, 3, 4, 6, 8, 12, 16,
17 20 and 24 hours after the devices were first activated. The patients were
18 asked to assess pain intensity by marking on a 10 cm long strip, containing a
19 scale of 1 to 100, with 1 being associated with no pain and 100 being
20 associated with the most severe intensity pain. The quality of analgesia was
21 evaluated by a categorical rating of excellent, good, fair or unsatisfactory
22 according to the same time schedule as that for the pain intensity
23 measurements.

24 The quality of analgesia and pain intensity data for the 53 patients
25 using the 40 µg dose electrotransport devices are shown in FIGS. 2 and 3,
26 respectively.

27 Skin sites beneath the anode and cathode gels were assessed
28 at 1, 6 and 24 hours following removal of the devices and evaluated for
29 topical (e.g., irritation) effects. The topical effects data are shown in Table 1

TABLE 1

Hours Post Removal	ETS Skin Site	Score	Edema (%)	Erythema (%)	Extent of Erythema (%)	Itching (%)	Papules (%)	Pustules (%)
1	Anode	0	74	15	19	91	92	100
		1	8	49	32	6	6	0
		2	19	36	49	4	2	0
	Cathode	0	92	72	74	94	94	100
		1	6	19	13	4	6	0
		2	2	9	13	2	0	0
6	Anode	0	74	15	17	89	92	100
		1	11	43	34	8	8	0
		2	15	40	49	4	0	0
		3	0	2	0	0	0	0
	Cathode	0	92	68	68	91	91	100
		1	4	19	13	9	6	0
		2	4	9	19	0	4	0
		3	0	4	0	0	0	0
24	Anode	0	83	34	36	91	96	98
		1	9	40	38	8	4	2
		2	8	28	36	2	0	0
		3	0	0	0	0	0	0
	Cathode	0	91	70	70	91	89	98
		1	6	19	15	8	8	0
		2	4	8	15	2	4	2
		3	0	4	0	0	0	0

Erythema: 0 = None

- 1 = Barely perceptible redness
- 2 = Definite redness
- 3 = "Beet" redness

Itching: 0 = None

- 1 = Mild
- 2 = Moderate
- 3 = Severe

Edema, Papules, Pustules, Extent of Erythema: 0 = None

- 1 = <50% of occluded area
- 2 = >50% of occluded area

EXAMPLE 2

Two fentanyl hydrochloride-containing anodic donor reservoir PVOH-based gels were made having the following compositions:

Donor Gel Formulations:

<u>Material</u>	<u>wt %</u>	<u>wt %</u>
Purified Water	86.3	85.3
Washed PVOH	12.0	12.0
Fentanyl HCl	1.7	1.7
Hydroxy Methylcellulose	---	1.0

With both formulations, the water and PVOH are mixed at a temperature between 92 °C and 98 °C followed by the addition of fentanyl hydrochloride and subsequent further mixing. The liquid gel was then pumped into foam molds having a disc-shaped cavity. The molds were placed in a freezer overnight at -35 °C to cross-link the PVOH. The gels can be used as anodic donor reservoirs suitable for transdermal electrotransport fentanyl delivery to achieve patient analgesia.

In summary, the present invention provides a device for improving the transdermal electrotransport of water soluble salts of fentanyl and sufentanil. The electrotransport device preferably has a silver anodic donor electrode and a hydrogel based donor reservoir. The electrotransport device is preferably a patient-controlled device. The hydrogel formulation contains a drug concentration which is sufficient to provide an acceptable level of analgesia.